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CONFERENCE REPORT
Weak Associations in Epidemiology and Their Interpretation[1]

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INTRODUCTION

With the increasing awareness that one's health is affected by environment and lifestyle, greater attention has been placed on the study of a variety of agents which might cause disease. While many of these agents may usefully be studied in the laboratory, it is largely left to epidemiologic investigation to determine whether humans are in fact at risk.

When cause and effect are strongly linked, and particularly when an effect also follows soon after a cause, the association is easily discovered. Lay or clinical observations have frequently proved sufficient to bring occupational risks to light, although epidemiologic investigation usually has been necessary to confirm and quantify the magnitude of the risk. When, however, an association between cause

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and effect is weaker or less obvious, particularly if the effect follows long after the cause, then epidemiologic investigations become essential, but difficult. Where the relationship between a factor and disease is weak, we are liable to establish an association when, in fact, none exists, or fail to find one when it does.

This paper arose from a workshop convened to examine these problems and to consider what methods can be used to strengthen the sensitivity of epidemiologic investigations.

When weak associations are observed, there will always remain areas of doubt requiring the application of judgment and experience before final conclusions can be drawn. Because chance or bias can easily produce a spurious weak association, the need to seek supporting evidence is greater with weak than with strong associations. For guidance, reference can be made to the five criteria for judging whether an association between an exposure and a disease is causal, which were published in the first report of the Advisory Committee to the Surgeon General on Smoking and Health (19).

(a) Consistency: Has or can the association be demonstrated repeatedly in different studies? Does the association occur consistently for different subgroups within the same study?
(b) Strength: Is the effect large? Is there a dose–response relationship, i.e., does the risk of developing the disease increase with increasing exposure?
(c) Specificity: Does the association link a single clearly defined exposure to a specified disease?
(d) Temporal sequence: Does exposure precede the disease?
(e) Coherence: Is the association biologically plausible? Are there animal or *in vitro* experimental data that suggest a reasonable mechanism, bearing in mind such considerations as the dose of the suspected causative agent, the site and duration of contact, and the metabolism of the agent?

There is one additional factor that is at times overlooked, namely, whether removal of a putative cause leads to a reduction in the incidence of disease. For example, the reduction in cigarette smoking by British physicians resulted in a striking reduction in their rates of lung cancer, thereby supporting the inference of a causal connection (5).

One measure of the strength of an association is the *relative risk,* which is defined as the risk of disease in an "exposed" group divided by the risk in an "unexposed" but otherwise comparable group. An "exposure" may represent past use of or exposure to a specified agent, or the presence of a particular factor or attribute. The term "relative risk" is generally used without reference to whether an association is causal, and in this paper the term "weak" refers to relative risks between 1.0 and 2.0 (or between 0.5 and 1.0 if a reduced risk were apparent). Thus, we are addressing situations in which an exposure produces at most a doubling or a halving of the risk of disease. By "interpretation" we mean the assessment of an association in terms of whether it is causal and, if so, what are the public health implications.

INCREASING THE SENSITIVITY OF EPIDEMIOLOGIC STUDIES

The sensitivity of a study is the probability that it will detect an underlying association. A direct approach to increasing sensitivity is to increase the number

of subjects studied. Figure 1 shows the probability with which one can detect an association in a retrospective (case-control) study according to the underlying relative risk and the number of subjects studied. For weak associations a very large number of subjects needs to be studied if the sensitivity is to exceed 50%.

A common mistake in the interpretation of epidemiologic data is that studies finding no associations based on a small number of subjects are interpreted as being negative, even though they may be consistent with a reasonably strong positive effect. Another error is the overinterpretation of positive results based on studies with a small number of subjects. With negative studies, it is always useful to calculate the sensitivity, as was done, for example, by Kessler and Clark in their investigation of artificial sweeteners and bladder cancer (11).

An advantage of large studies is that one can examine subgroups, particularly those stratified according to varying exposure levels of the agent being studied. Problems often arise, however, in the interpretation of findings resulting from subgroup analysis. A study with an overall relative risk of about 1.0 (i.e., no alteration in risk associated with exposure) may have a particular subgroup in which the relative risk is much greater. This occurred, for example, in a large case-control study of artificial sweeteners and bladder cancer (10), which was based on 3,010 cases and nearly twice as many controls. No statistically significant increased risk of bladder cancer due to artificial sweetener use was observed in the study group as a whole, and numerous inconsistencies were noted in the analysis of the dose–response relationships. A positive relationship was found among nonsmoking women, however. Was the finding real, or did it occur by chance, especially in view of the search for an effect among many possible subgroups? In attempting to answer this question, one should apply the previously mentioned criteria for judging whether an association is causal. If the answer cannot be well supported from the data at hand, the apparent high risk in the

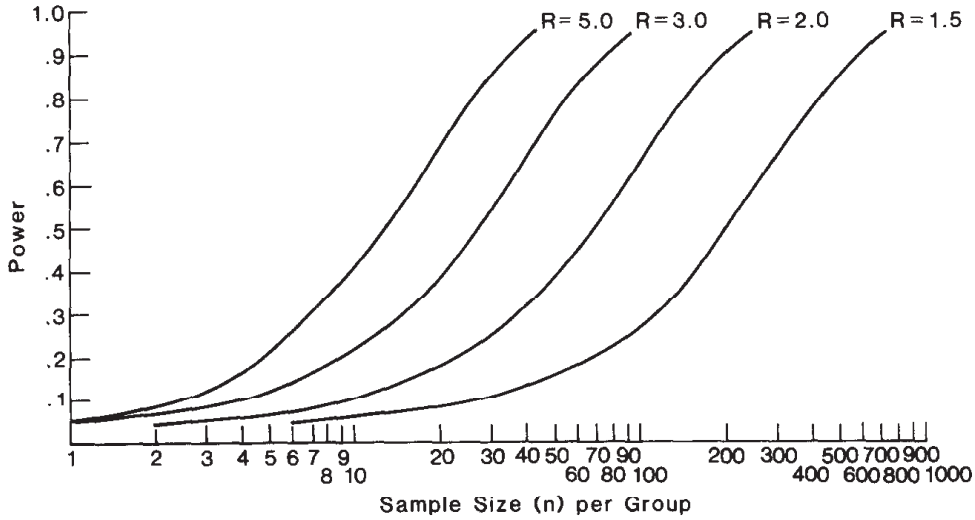

FIG. 1. Power of a case-control study as a function of sample size per group (N) and relative risk. Calculations assume a two-sided test of significance at the $\alpha = 0.05$ level and a 30% exposure rate among controls.

subgroup should not be overemphasized. One should rather attempt to confirm or refute the finding by further study, which is often best done in a different manner from the original investigation.

If it is not practical to conduct a large study in order to investigate a suspected weak association, the sensitivity can be increased by identifying subgroups in the population with an unusually high level of exposure to the suspected causal agent. Exposures which occur in the occupational environment are often greater than those which occur in the community, so that a comparison of highly exposed workers with unexposed individuals in the community can often be particularly instructive. As with any comparison of this sort, in order to rule out spurious associations, one needs to bear in mind risk factors other than the study exposure that may differ in the groups.

Other subgroups which may be studied to increase the sensitivity of a study will depend on how the agent being studied might interact with other agents which cause the disease in question. As an example, if an agent such as asbestos is thought to interact *multiplicatively* with tobacco smoking as a cause of lung cancer (17), then the study is more likely to yield positive results among smokers than among nonsmokers. If the agent being studied acts *additively* rather than multiplicatively with other agents causing the same disease, it may be preferable to choose a group which has a low underlying risk of disease. For example, heart disease is strongly associated with cigarette smoking among the young, but only weakly associated with cigarette smoking among the old, among whom other causes of coronary heart diseases are relatively more contributory (9). Thus, the study of smoking and heart disease is more likely to yield positive results among a study population of young subjects than among a group of elderly subjects.

BIAS

Bias can be defined as systematic error in the design or conduct of a study that leads to an incorrect assessment of risk. Sackett (16) has catalogued numerous types of bias that can occur in epidemiologic studies, so that only certain examples will be listed here for illustrative purposes.

In case-control studies in which patients with the study disease (cases) are compared with individuals who are free of the disease under study (controls), the manner by which subjects are ascertained may be biased. For example, consider a study of phlebitis in relation to oral contraceptive use. If there is a suspicion among physicians that oral contraceptive use may cause phlebitis, patients with leg pain who are on oral contraceptives might be more likely to be referred for diagnostic investigation. As a consequence, oral contraceptive users with leg pain would be more likely to be diagnosed with phlebitis and enter the case group, as compared with non-oral contraceptive users with leg pain. If this occurred, an overestimate of the effect of oral contraceptives would be obtained.

As another example of ascertainment bias, an industry with excellent medical services may have a high incidence of a type of cancer that is difficult to diagnose, such as cancer of the pancreas, when compared with the general population. This could result from differences in diagnostic facilities and record keeping, which would need to be considered in any assessment of the study findings.

When obtaining information based on personal interviews, an investigator should recognize that some subjects may selectively recall information unconsciously, to please the interviewer, or to conceal information. Furthermore, some interviewers may probe more diligently for items in taking a history from diseased individuals than from the controls because of inadequate training or prior knowledge of the hypotheses.

Finally, bias can be introduced into a study by the investigator who, favoring a particular hypothesis, restricts the analysis and reporting of results to instances that confirm his presumptions, underplaying or ignoring analyses that negate them.

Bias as It Affects Weak Associations

Although there are no special considerations regarding the likelihood of bias in studies with weak associations, it is of greater concern because even a small bias may account entirely for the association, thereby resulting in an incorrect causal inference. In a study where a strong association has been found, knowledge of bias may force an investigator to alter the assessment of the magnitude of risk, but it rarely requires a reversal of conclusions.

Controlling, Measuring, and Minimizing Bias

When starting an epidemiologic study, the investigator should list potential sources of bias, try to estimate the extent to which they may occur, and attempt to devise strategies to minimize, eliminate, or measure them. If certain biases seem likely to be so extreme that no strategy can be adopted to minimize or remove them, the investigator may have to decide that the study is not worth starting.

Certain strategies can be adopted for avoiding bias. Ascertainment bias in case-control studies can be minimized or measured by learning more about the circumstances by which the disease is identified and medical care received by the newly found cases. (Similar attention should be given to the selection of controls.) Recall bias can be reduced through the use of standardized questionnaires, and can occasionally be detected through a comparison of responses with preexisting records. To reduce interviewer bias, interviewers can be trained to probe even-handedly when obtaining histories and occasionally can be kept ignorant of the hypotheses being tested.

CONFOUNDING

The term *confounding* refers to the effect of an extraneous variable that wholly or partially explains the apparent effect of the study exposure. Thus an apparent association between two variables, A and B, may actually be due to a third variable C (the confounding variable), which is associated with both A and B. For example, consider a study of the effect of some industrial exposure on lung function. Lung function might be compared in exposed and nonexposed groups. If lung function is found to be lower in the exposed group, the conclusion might be drawn that exposure had caused the reduced function. Suppose, however, that the exposed group is older than the nonexposed group and that lung function declines with age. As a consequence, the lower function that has been found in the exposed

group might be partly or completely due to age. If this were the case, one would say that the apparent effect of exposure is partly or completely "confounded by" the effect of age.

A confounder (confounding variable) satisfies both of two conditions: (a) it is a risk factor for the study disease, and (b) it is associated with exposure to the agent under study, but is not a consequence of such exposure.

Confounding can increase an apparent difference between two comparison groups if the effect of confounding contributes to the effect of the variable of interest. Confounding may, however, mask a weak association if the apparently causative factor is negatively associated with the confounder. As an example, consider a case-control study of myocardial infarction in relation to recent oral contraceptive use (18). Cases admitted to hospital with a diagnosis of myocardial infarction will tend to be older than controls selected from admissions for acute conditions such as trauma and gastrointestinal disorders. Because recent use of oral contraceptives is more likely among the younger women, failure to adjust the comparison of oral contraceptive use in cases and controls will underestimate the relative risk. For the study cited (18) the age-adjusted estimate of relative risk is $R = 3.97$; ignoring age results in a spuriously low estimate of $R = 1.68$.

Identifying Confounding Factors

In order to identify confounding factors, it is important to know the epidemiology of the disease being studied. Any factor which is known to affect the risk of the study disease is a possible confounder. Although an exact specification of confounding factors will depend on the particular circumstances of a study, age, sex, race, socioeconomic status, smoking habits, and place of residence are factors which usually need to be considered in the design of any investigation. Many other factors will, of course, have to be considered in relation to specific diseases. For instance, cigarette smoking and coffee consumption are highly correlated habits. Thus one has to control carefully for one variable to determine the possible independent health effects of the other. To take another example, air pollution data are particularly susceptible to being influenced by confounders. When the air is highly polluted in one area of a city, its population is likely to be of lower socioeconomic status. Thus, life-style variables related to income would be different from those in the general population of the city.

Control of Confounding

Control of confounding can be achieved either in the design of a study or in its analysis, provided that one can identify and measure the confounding factors, and that the confounding is not "complete" (i.e., the study factors and the confounder do not always occur together, so that one can separate their individual effects). The need to control for a confounding variable by matching, stratification, or multivariate analysis depends on whether it has any residual association with exposure and disease after adjustment for other factors included in the analysis or sampling schemes. With correlated variables, adjustment for one may effectively dispose of the need to adjust for the other.

The design of a study should either eliminate or allow for the assessment of all

major confounding factors. Thus, one might control for age by restricting the study to a particular age group, by drawing a sample which is stratified by age, or by matching on the basis of age.

Matching is commonly used to control for important known confounders. Although this technique assures that the comparison groups are comparable on the variables used for matching, it also precludes study of their influence on the disease in question. Thus, the choice of variables to be matched should be made with care. In practice, the cost and feasibility of matching often restrict its application to a relatively few characteristics (14).

In any study, one should ensure that data are collected on all important potentially confounding variables. This allows one to deal with confounders in the analysis by using statistical adjustment procedures based on stratification or multivariate models. As a first step, one can compare the crude and the adjusted estimates of relative risk using the Mantel Haenszel technique (13). "Large" differences between the crude and adjusted estimates suggest a need for adjustment. This approach, which uses stratification based on potential confounders, allows one to differentiate the more important factors from the less important, and permits an assessment of the effects due to confounding. The main problem that arises is that progressive stratification quickly leads to problems of small numbers in different subgroups, in which case statistical methods based on multivariate models are available to make adjustments for confounders (20). These techniques are not without their own problems, however. They need to be applied judiciously and with understanding if errors and incorrect conclusions are to be avoided (7, 8).

A good example of the use of stratification to control for confounding is provided by a study of the relationship between alcohol consumption and cancer of the mouth (15). Tobacco smoking was known to be an important cause of oral cancer. Furthermore, smoking and the consumption of alcohol were well known to be associated. Consequently, the confounding of an effect of alcohol by smoking had to be avoided. This was done by first stratifying subjects on the basis of smoking (four categories) and then examining alcohol consumption (four categories) within each smoking subgroup.

Table 1 shows the estimates of the relative risk of oral cancer for various combinations of smoking and alcohol consumption. All risks are expressed as ratios relative to the group of individuals who neither smoked nor drank. The

TABLE 1

RELATIVE RISK OF ORAL CANCER ACCORDING TO LEVEL OF EXPOSURE TO ALCOHOL AND SMOKING

Alcohol per day (oz)	Cigarette equivalents per day			
	0	<20	20–39	40+
None	1.00[a]	1.52	1.43	2.43
<0.4	1.40	1.67	3.18	3.24
0.4–1.5	1.60	4.36	4.46	8.21
>1.5	2.33	4.13	9.59	15.5

Source: Rothman and Keller (15).

[a] Reference group.

effect of alcohol consumption (in the absence of smoking) is evaluated by looking down the first column. The effect of smoking (in the absence of alcohol consumption) is evaluated by looking across the first row. The combined effect of both smoking and drinking is represented by the other entries in Table 1.

Note the evidence of a dose–response relationship for both smoking and alcohol consumption. For example, the risk of cancer increases progressively (with one exception) with increasing amounts of alcohol consumed per day. This relationship holds within each of the smoking subgroups. A similar dose–response relationship occurs for smoking. Finally, the very high relative risks shown in the highest smoking and drinking categories suggest an interaction between them in the production of this form of cancer.

Problems of Confounding

Care should be taken that adjustments not be made for the effect of an apparently confounding variable if that variable is likely to intervene between the factor of interest and the study disease. In this circumstance, an adjustment would spuriously diminish the effect of the study factor. For example, if a study is concerned with the relation of air pollution to overall mortality, then differences in the occurrence of influenza, itself a cause of death, might be considered to be a confounding factor in a comparison among cities. However, if air pollution increased one's susceptibility to influenza, then an adjustment for differences in the rates of influenza would spuriously reduce the estimated effect of air pollution on mortality.

Confounding may also be inadequately controlled if measurement of the confounder is relatively nonspecific. Thus, a simple classification of individuals as "smokers" or "nonsmokers" is likely to eliminate only partially a confounding effect due to cigarette smoking. Inadequate control may also occur if the confounder has many components, only one of which actually affects the risk of disease. Social class is such a factor. It reflects family income, occupation, level of education, quality of housing, crowding, opportunity for respiratory infections and other diseases, and so forth. Matching or stratification of subjects on the basis of social class is thus unlikely to control completely for any one of the factors which it reflects. In some circumstances, only a randomized intervention study may eliminate conclusively the effects of confounders.

Confounding is sometimes considered in major comparisons but ignored when subgroups are studied. This error must be carefully avoided. In spite of all attempts to control for confounding, one must recognize that there may be confounding factors which have not been identified. Such unknown or undetected confounders might eliminate a 50% alteration in risk (relative risks between 1.0 and 1.5, or between 0.5 and 1.0), but they are unlikely to completely eliminate changes of a larger magnitude (1, 2).

ASSESSING RISK TO THE COMMUNITY

Once a weak association between a specific exposure and a given disease has been identified and established as unlikely to be due to chance, bias or confounding, one should estimate the effect of this risk on the community, a process which

has been loosely termed "risk assessment." This step is important in determining the public health consequences of exposure. It is frequently performed inappropriately, however.

The main objective of risk assessment is to determine how many cases of disease in the population result from the exposure under study. To accomplish this, two items of information are needed: (a) an estimate of the extent of exposure, and (b) an estimate of the relationship between exposure and the risk of death or disease.

Estimate of Exposure

A precise estimate of exposure is usually difficult to achieve; estimates often are limited and crude. We are particularly handicapped by inadequacy of past measurements. This is true for past occupational exposures which will often not have been measured, exposure to air pollution or to carcinogens which are newly found in drinking water, past dietary consumption or personal habits, exposure to ionizing radiation, and so forth. Not only is the intensity and duration of exposure needed, but also an indication of the number of people so exposed. One may be concerned with continuous exposure to low doses of an agent over some segment of the lifespan or with an acute high dose at an instant in time. Since the effect of an exposure is often modified substantially by other factors, such as age and sex, one will often have to incorporate additional variables into the analysis. This usually leads to the adoption of some exposure model in order to proceed with risk assessment.

Estimate of Risk

To quantify risk of disease due to exposure, several questions need to be dealt with.

(a) What is the dose–response relationship between exposure and the risk of disease? If the dose–response relationship is linear, then a unit increase in dose produces the same effect on risk at high doses as it does at low doses. If the dose–response relationship is more complex, then a unit increase in dose will place some people at proportionally higher risk than others. For example, if the dose–response relationship were curved upward, the risk of disease would be elevated more by a given extra amount of exposure at high levels of exposure than at low levels. Such knowledge could affect the drafting of regulations designed to set safe limits of exposure. Thus, if some effects of carbon monoxide exposure followed such a curvilinear relationship, smokers, because of their higher baseline exposure resulting from smoking, would be at greater risk from environmental sources of carbon monoxide than nonsmokers. The additional increase in carboxyhemoglobin from environmental sources would have a greater effect for smokers than the same increase for nonsmokers.

(b) Are there subgroups of individuals who are particularly at risk because they are especially sensitive to the agent? If such groups could be identified, special efforts could be taken to protect them from exposure. For example, individuals homozygous for diseases associated with deficiencies in DNA repair generally can be readily identified and could be protected individually from exposure to muta-

gens or carcinogens. However, if persons heterozygous for this condition also proved to be at higher risk of cancer or transmissable genetic diseases resulting from exposure to such agents, they would be a large group at special risk that could be difficult to identify in advance.

(c) Is the effect of duration of exposure known? If the estimate of risk varies with the duration of exposure, it is necessary to ensure that the correct estimate is applied to the population as a whole. For example, suppose that most people have been exposed to asbestos on only one or two isolated occasions, while sawing asbestos board, for example. If the estimate of the risk of lung cancer from exposure to asbestos is based upon individuals with many years of chronic exposure, it would be invalid to apply this estimate of risk to the general population of exposed individuals.

Is there a lag time before an exposure manifests its effect? Some substances, particularly carcinogens or dusts, may take many years to exert their full effect, so that an estimate of risk within a few years of exposure is likely to be small in comparison with an estimate made after many years of exposure. A recent report (6) on the avoidable risks of cancer provides an excellent discussion of these and other considerations in quantitative risk assessment.

Estimation of the Proportion of Deaths or Cases of Disease in a Population Which Are Attributable to Exposure

From an estimate of relative risk linking, say, cigarette smoking to coronary heart disease, it is possible to determine the number (or the proportion) of excess deaths that are attributable to the exposure, provided that the proportion of the population exposed is known. Of course, in extrapolating an estimate of risk based on a study population to the general population of interest, one has to be sure that the extent and duration of exposure in the general population is similar to that in the study population. If the conditions are not similar, one can sometimes make proper allowance for differences by means of a dose–response model.

Rather than study mortality exclusively, often it is necessary also to study disease incidence. This can be important when the people affected die from causes unrelated to the study exposure. For example, industrial exposure to dust can cause severe and disabling lung disease, but may not lead to death.

As a simple example of the calculations involved, assume that 60% of adult males smoke cigarettes. From an American Cancer Society prospective study, the annual death rate from coronary heart disease among men aged 45–54 years was 958 per 100,000 for cigarette smokers, and 406 per 100,000 for nonsmokers (9). If no one smoked, then one would expect 406 coronary heart disease deaths to occur among 100,000 men aged 45–54 years instead of the 737 deaths observed when 60% are smokers (see Table 2). Thus, 331 of the 737 observed deaths, or 45% of the deaths due to coronary heart disease, are attributable to cigarette smoking.

In this example the coronary heart disease death rates are known for those who smoked cigarettes and for those who did not. In fact, only the ratio of the rates (i.e., the relative risk) and the proportion of cigarette smokers in the population need to be known to perform the calculation. Given an estimate of the relative risk (R) and the proportion of individuals in the population who are exposed (X), the

TABLE 2
CIGARETTE SMOKING AND DEATHS DUE TO CORONARY HEART DISEASE

Number of men	Cigarette smoking habits	Death rate from CHD per 100,000 per year	Number of cases
100,000	60,000 smokers	958	575
	40,000 nonsmokers	406	162
Total			737

Source: Based on data from the American Cancer Society prospective study (6).

proportion (P) of all deaths or disease which are attributable to the exposure can be determined from (3, 12):

$$P = (R-1)X/[1+(R-1)X]. \quad [1]$$

Table 3, which is based on Eq. [1], shows as a function of R and X the percentage of deaths or cases of disease in a population which are attributable to an exposure ($P \times 100\%$). Weak associations ($R \leq 2$) can nevertheless be important in public health terms if an exposure is rather common ($X \geq 0.25$) in the population at large.

In the above discussion we have used two methods of comparing rates of mortality in two groups of people; one rate was subtracted from the other to determine the *absolute* difference between the two rates, or one rate was divided by the other to give the *ratio* of one to another. In general, the absolute difference between two rates ("excess mortality") is of public health importance, since it indicates the number of extra deaths that result from the factor in question. The ratio of the rates (the "risk ratio" or "relative risk") indicates the strength of the association and hence is more useful in judging whether the association might be causal (4).

A serious problem can arise when applying an estimate of relative risk derived from a specific study to the general population. The estimate of relative risk is often derived from a heavily exposed group which will have been selected to

TABLE 3
POPULATION ATTRIBUTABLE RISK (%) AS A FUNCTION OF THE RELATIVE RISK (R) AND THE PROPORTION OF THE POPULATION EXPOSED (X)

Proportion exposed (X)	Relative risk (R)			
	1.5	2	5	10
0.01	0.5	1	4	8
0.05	2	5	17	31
0.10	5	9	29	47
0.25	11	20	50	69
0.5	20	33	67	82
0.9	31	47	78	89

maximize the chances of identifying a possible risk. Such an estimate should not be directly transferred to less heavily exposed groups or to groups exposed for a shorter period of time, otherwise the attributable risk will be overestimated.

Further difficulties in estimating the effect of an exposure on the community at large often derive from an incomplete understanding of environmental, behavioral, or genetic factors that may enhance or diminish the effect of the study exposure. As a consequence, an estimate of risk to the community in general may be inexact (21, 22).

CONCLUSION

Epidemiologic studies are designed to determine whether humans are at risk of developing disease when exposed to an environmental factor, to assess the magnitude of risk, and to estimate the reduction in disease that would occur if the factor were eliminated or exposure to it reduced. Epidemiology is thus concerned with issues that have important scientific, social, and economic implications. In this brief presentation some concepts have been reviewed that should help one to evaluate critically reports of epidemiologic investigations. It should also remind epidemiologists of some of the principles to be used in assessing their findings and communicating results of studies suggesting weak associations. It is incumbent upon them to practice their science with the greatest of care because the results of their studies, for better or for worse, are affecting the future environment in which humans hope to live and prosper.

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